PCT/EP 03/14867

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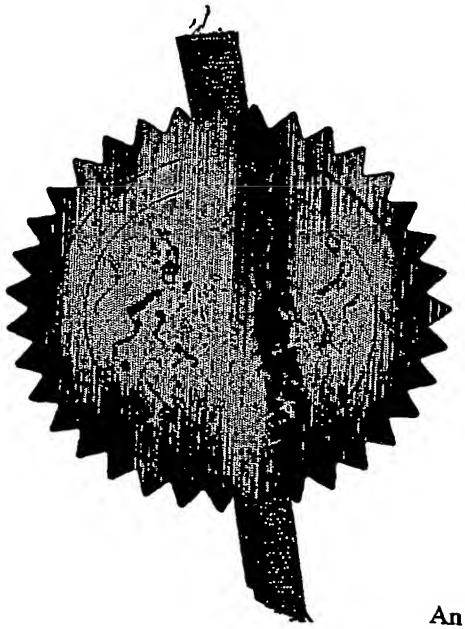

Signed Stephen Hordley

Dated 2 December 2003

Pater Form 1/77

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27DEC02 E773413-1 D01030
P01/7700 0.00-0230045.7

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

23 DEC 2002

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — REHH/NM/P33153

2. Patent application number
(The Patent Office will fill in his part) — 0230045.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* 00473587003

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 07960988003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	5
Claim(s)	0
Abstract	0
Drawings	0

10: If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

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11. We request the grant of a patent on the basis of this application

Signature R E H Hackett Date 23-Dec-02

R E H Hackett

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12. Name and daytime telephone number of person to contact in the United Kingdom

R E H Hackett 01438 768534

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Notes

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b) Write your answers in capital letters using black ink or you may type them.

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d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

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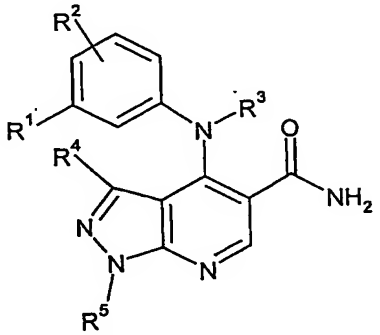
COMPOUNDS

The present invention relates to pyrazolopyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolopyridine compounds in therapy, for example as inhibitors of phosphodiesterases (PDE) and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma or allergic rhinitis.

US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic agents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

Japanese laid-open patent application JP-2002-20386-A (Ono Yakuhin Kogyo KK) published on 23 January 2002 discloses pyrazolopyridine compounds of the following formula:



JP-2002-20386-A
(Ono)

wherein R^1 denotes 1) a group $-OR^6$, 2) a group $-SR^7$, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by a hydroxy group or a C1-8 alkoxy group, 7) a phenyl group, 8) a group $-C(O)R^8$, 9) a group $-SO_2NR^9R^{10}$, 10) a group $-NR^{11}SO_2R^{12}$, 11) a group $-NR^{13}C(O)R^{14}$ or 12) a group $-CH=NR^{15}$. R^6 and R^7

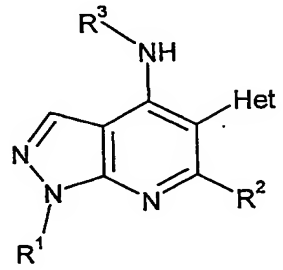
denote i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by a phenyl group or vii) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group. R^3 denotes 1) a hydrogen atom or 2) a C1-8 alkyl group. R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group or 5) a phenyl group which may be substituted by 1-3 substituents. In group R^3, a hydrogen atom is preferred. In group R^4, methyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl are preferred. The compounds of JP-2002-20386-A are stated as having PDE4 inhibitory activity and as being useful in the prevention and/or treatment of inflammatory diseases and many other diseases.

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

The compound cartazolate is known (ethyl 1-ethyl-4-n-butylamino-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate). J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives and their affinities at A_1- and A_{2A}-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the $GABA_A$-receptor channel. S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531 disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A1-adenosine receptor ligands.

It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

The present invention provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):



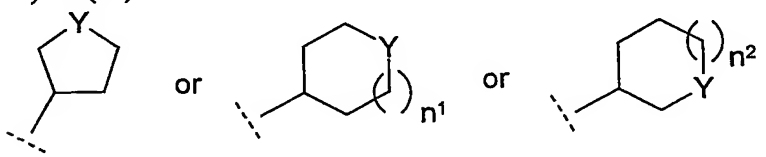
(I)

wherein:

R^1 = a hydrogen atom, C_{1-4}alkyl, C_{1-3}fluoroalkyl or $-(CH_2)_2OH$;

R^2 is a hydrogen atom, methyl or C_1fluoroalkyl;

R^3 is optionally substituted C_{1-8}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted phenyl, or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc):



(aa) (bb) (cc)

in which n^1 and n^2 are 1 or 2; and Y is O, S, SO_2, or NR^4; where R^4 is a hydrogen atom, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $C(O)NH_2$, $C(O)$-C_{1-2}alkyl, or $C(O)$-C_1fluoroalkyl; provided that Y is not NR^4 when the heterocyclic group is of sub-formula (aa);

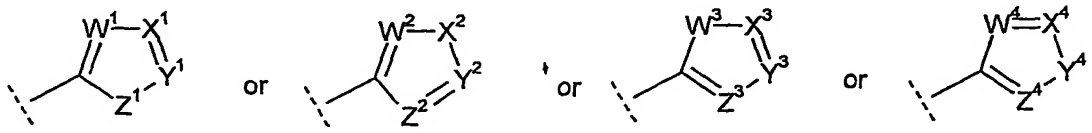
wherein in R^3 the C_{1-8}alkyl is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy or C_{1-2}fluoroalkoxy; and wherein any such substituent is not substituted at the R^3 carbon atom attached to the -NH- group of formula (I);

wherein in R^3 the phenyl is optionally substituted with one substituent being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano;

wherein in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy, or C_{1-2}alkyl; and wherein any OH, alkoxy or fluoroalkoxy substituent is not substituted at the R^3 ring carbon attached to the -NH-

group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc); and

and wherein Het is of sub-formula (i), (ii), (iii) or (iv), preferably of sub-formula (i):



(i) (ii) (iii) (iv)

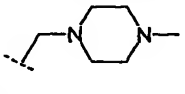
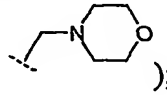
wherein:
W^1, W^2 and W^4 is N; and W^3 is NR^W ;

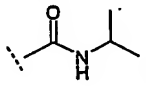
X^1, X^3 and X^4 is N or CR^X (preferably N); and X^2 is O, S or NR^X ;

Y^1, Y^2 and Y^3 is CR^Y or N (preferably CR^Y); and Y^4 is O, S or NR^Y ;

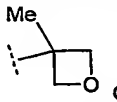
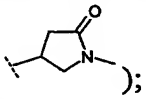
Z^1 is O, S or NR^Z (preferably Z^1 is O or S); and Z^2, Z^3 and Z^4 is N or CR^Z;

wherein:
R^W is a hydrogen atom (H) or C_{1-2}alkyl (more preferably H);

R^X and R^Y independently are:
a hydrogen atom (H);
C_{1-8}alkyl (e.g. C_{1-6}alkyl e.g. C_{3-6}alkyl and/or C_{1-4}alkyl such as methyl, isopropyl, isobutyl or t-butyl);
C_{3-6}cycloalkyl (e.g. cyclopropyl);
$-(CH_2)_{n^3}-SO_2-R^5$ wherein n^3 is 1 or 2 and R^5 is C_{1-3}alkyl or $-NH-C_{1-2}$alkyl (e.g. CH_2SO_2Me);
$-(CH_2)_{n^4}-NR^6R^7$ wherein n^4 is 0, 1 or 2, and R^6 and R^7 independently are H, C_{1-6}alkyl e.g. C_{1-4}alkyl, $-C(O)-C_{1-2}$alkyl or $-SO_2-C_{1-2}$alkyl (in which case preferably R^6 is H and/or and R^7 is C_{1-6}alkyl e.g. C_{1-4}alkyl); or R^6 and R^7 together are $-(CH_2)_{n^5}-X^5-(CH_2)_{n^6}-$ in which n^5 and n^6 independently are 2 or 3 and X^5 is a bond, $-CH_2-$, O, NR^8 wherein R^8 is H or C_{1-2}alkyl (e.g. preferably n^4 is 0 or 1; and/or preferably n^5 and/or n^6 are 2; and/or $-(CH_2)_{n^4}-NR^6R^7$ preferably can be NMe_2 or  or );
$-(CH_2)_{n^7}-O-R^9$ wherein wherein n^7 is 1 or 2 and R^9 is H or C_{1-6}alkyl e.g. C_{1-4}alkyl (e.g. n^7 is preferably 1 and/or R^9 is preferably methyl or t-butyl);

-C(O)-$NR^{10}R^{11}$ wherein R^{10} and R^{11} independently are H or C_{1-6}alkyl (in which case preferably R^{10} is H and/or and R^{11} is C_{1-6}alkyl e.g. C_{1-4}alkyl such as isopropyl); or R^{10} and R^{10} together are -$(CH_2)_n{}^8$-X^6-$(CH_2)_n{}^9$- in which n^8 and n^9 independently are 2 or 3 and X^6 is a bond, -CH_2-, O, NR^{12} wherein R^{12} is H or C_{1-2}alkyl (e.g. -C(O)-$NR^{10}R^{11}$ can be );

-C(O)-OR^{13} wherein R^{13} is H or C_{1-6}alkyl e.g. C_{1-4}alkyl in particular methyl or ethyl;

a 4-, 5-, 6- or 7-membered saturated heterocyclic ring containing one O ring atom or one NR^{14} ring group wherein R^{14} is H or C_{1-4}alkyl e.g. C_{1-2}alkyl, said heterocyclic ring (other than at any NR^{14} position) being optionally substituted by one oxo (=O) and/or one C_{1-4}alkyl e.g. C_{1-2}alkyl substituent (e.g. the optionally substituted saturated heterocyclic ring can be tetrahydropyran-4-yl or  or );

-$(CH_2)_n{}^{10}$-Ar wherein n^{10} is 0, 1 or 2 and

(i) Ar is phenyl optionally substituted by one or two substituents being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano; or

(ii) Ar is an optionally substituted 5- or 6-membered heterocyclic aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N or S; and wherein when the heterocyclic aromatic ring Ar contains 2 or 3 heteroatoms, one is selected from O, N and S and the remaining heteroatom(s) are N; and wherein the heterocyclic aromatic ring Ar is optionally substituted by one or two C_{1-4}alkyl groups (for example: Ar when a heterocyclic aromatic ring can be optionally substituted furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, imidazolyl, oxadiazolyl (e.g. 1,3,4- or 1,2,4- oxadiazolyl), thiadiazolyl (e.g. 1,3,4- or 1,2,4-), pyridyl, triazolyl (e.g. 1,2,4-triazolyl), triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, isothiazolyl (1,2-thiazolyl), and isoxazolyl (1,2-oxazolyl);

and

R^Z is a hydrogen atom (H) or C_{1-2}alkyl (more preferably H).

In compounds, for example in the compounds of formula (I), an "alkyl" group or moiety may be straight-chain or branched. Alkyl groups, for example C_{1-8}alkyl or C_{1-6}alkyl or C_{1-4}alkyl or C_{1-2}alkyl, which may be employed include C_{1-6}alkyl or C_{1-4}alkyl or C_{1-2}alkyl such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and

any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 3-methylbutan-2-yl, 2-ethylbutan-1-yl, and the like.

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C_{1-6}alkoxy or C_{1-4}alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above. "Alkylsulfonyl" such as C_{1-4}alkylsulfonyl includes methylsulfonyl (methanesulfonyl), ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C_{1-4}alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C_{3-8}cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferably, a C_{3-8} cycloalkyl group is C_{3-6}cycloalkyl or C_{5-6}cycloalkyl, that is the cycloalkyl group contains a 3-6 membered or 5-6 membered carbocyclic ring respectively.

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, etc. "Fluoroalkoxy" includes C_{1-4}fluoroalkoxy or C_{1-2}fluoroalkoxy such as trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C_{1-4}fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom ("halo") present in compounds, for example in the compounds of formula (I), can be a fluorine, chlorine, bromine or iodine atom ("fluoro", "chloro", "bromo" or "iodo").

Preferably, R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl or $-(CH_2)_2OH$; more preferably C_{1-3}alkyl, C_{1-2}fluoroalkyl or $-(CH_2)_2OH$; still more preferably C_{2-3}alkyl, C_2fluoroalkyl or $-(CH_2)_2OH$; and yet more preferably C_2alkyl or C_2fluoroalkyl. When R^1 is C_{1-4}alkyl or C_{1-3}fluoroalkyl, it can be straight-chained or branched. R^1 can for example be methyl, trifluoromethyl, ethyl, n-propyl, isopropyl, isobutyl, C_2fluoroalkyl or $-(CH_2)_2OH$; and more preferably R^1 is ethyl, n-propyl, C_2fluoroalkyl or $-(CH_2)_2OH$. R^1 is most preferably ethyl.

Preferably, R^2 is a hydrogen atom (H).

Where R^3 is optionally substituted phenyl, the optional substituent can be at the 2-, 3- or 4-position of the phenyl ring, e.g. at the 4-position. For example, R^3 can be phenyl or fluorophenyl; in particular 4-fluorophenyl.

R^3 is preferably optionally substituted C_{1-8}alkyl, optionally substituted C_{3-8}cycloalkyl, or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc). Preferably, in R^3 there is one substituent or no substituent.

Where R^3 is optionally substituted C_{1-8}alkyl, it is preferably optionally substituted C_{1-6}alkyl or more preferably optionally substituted C_{3-6}alkyl. In these 3 cases, preferably R^3 is unsubstituted alkyl such as n-propyl, isopropyl, isobutyl, sec-butyl, n-butyl, t-butyl, 3-methylbutan-2-yl, or 2-ethylbutan-1-yl. Where R^3 is optionally substituted C_{1-8}alkyl, it is most preferably isobutyl, sec-butyl, t-butyl or 3-methylbutan-2-yl (for example (R)-3-methylbutan-2-yl or (S)-3-methylbutan-2-yl).

In one embodiment, where R^3 is optionally substituted C_{3-8}cycloalkyl, it is not optionally substituted C_5cycloalkyl, i.e. not optionally substituted cyclopentyl. In this case, more preferably, R^3 is optionally substituted C_{6-8}cycloalkyl.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, it is more preferably C_6cycloalkyl (i.e. cyclohexyl) optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy, or C_{1-2}alkyl, and wherein any OH, alkoxy or fluoroalkoxy substituent is not substituted at the R^3 ring carbon attached to the -NH- group of formula (I). The preferred optional substituent is OH or oxo.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents if present preferably comprises (e.g. is) a substituent at the 3-, 4- or 5- position of the R^3 cycloalkyl ring. Any OH substituent is more preferably at the 3- or 5-position of the R^3 cycloalkyl ring. (In this connection, the 1-position of the R^3 cycloalkyl ring is deemed to be the connection point to the -NH- in formula (I)). Optionally, in R^3, the C_{3-8}cycloalkyl is unsubstituted.

Where R^3 is optionally substituted C_{3-8}cyclohexyl, R^3 is still more preferably cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O), OH, C_{1-2}alkoxy or C_{1-2}fluoroalkoxy substituent. The substituent is preferably at the 3-, 4- or 5- position of the R^3 cyclohexyl ring; more preferably any OH substituent is preferably at the 3- or 5-position of the R^3 cyclohexyl ring.

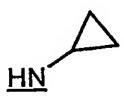
Where R^3 is optionally substituted C_{3-8}cyclohexyl, R^3 is most preferably cyclohexyl (i.e. unsubstituted) or 3-hydroxy-cyclohexyl or 4-oxo-cyclohexyl.

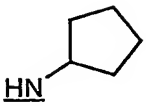
Where R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then preferably Y is O, S, SO_2 or N-C(O)-Me, more preferably O or N-C(O)-Me. (In the last case, R^4 is

-C(O)-Me). This is provided that R^3 is not N-C(O)-Me when the heterocyclic group is of sub-formula (aa).

In R^3, suitably the heterocyclic group is of sub-formula (bb). In sub-formula (bb), n^1 is preferably 1. In sub-formula (cc), n^2 is preferably 1. That is, six-membered rings are preferred in the R^3 heterocyclic group.
Preferably, in R^3, the heterocyclic group of sub-formula (aa), (bb) or (cc) is unsubstituted.

Preferably, NHR^3 is of sub-formula (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (L), (m), (n), (o), (p), (q), (r), (s) or (t):


(a)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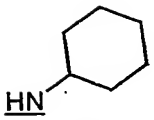
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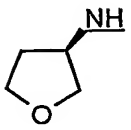
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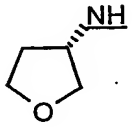
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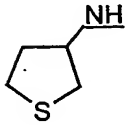
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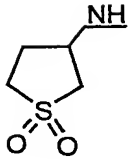
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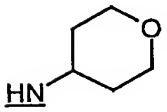
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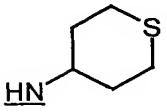
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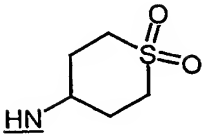
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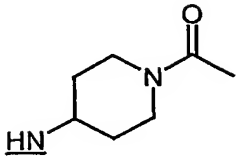
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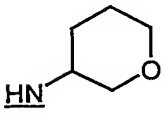
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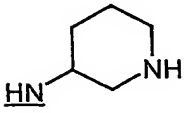
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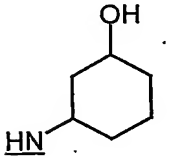
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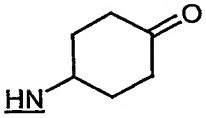
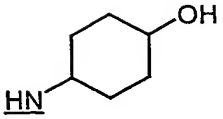
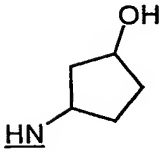
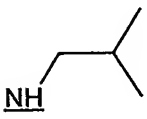

(o)


(p)


(q)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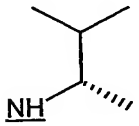
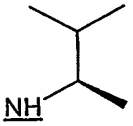

(s)


(t)

In the sub-formulae (a) to (t) etc above, the -NH- connection point of the NHR^3 group to the 4-position of the pyrazolopyridine of formula (I) is underlined.

Preferably, NHR^3 is of sub-formula (c), (d), (e), (f), (h), (i), (j), (k), (n), (o), (p), (q), (r), (s) or (t). More preferably NHR^3 is of sub-formula (c), (h), (k), (n), (o), (r), (s) or (t). Most preferably, R^3 is tetrahydro-2H-pyran-4-yl; that is NHR^3 is most preferably of sub-formula (h), shown above.

Preferably, one of R^X and R^Y is C_{1-2}alkyl or more preferably a hydrogen atom (H).

It is most preferred that the compound of formula (I) or the salt thereof is:

N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-(4-fluorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-5-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-isobutyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-isobutyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclohexyl-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-isobutyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1S)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1R)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,

1-Ethyl-N-isobutyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-{3-[(Dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-{5-[(4-methylpiperazin-1-yl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-isopropyl-1,3,4-oxadiazole-2-carboxamide,
4-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-1-methylpyrrolidin-2-one,
1-Ethyl-N-tetrahydro-2H-pyran-4-yl-5-(5-tetrahydro-2H-pyran-4-yl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(morpholin-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-[5-(Tert-butoxymethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine, or
methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3-oxazole-4-carboxylate;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts. A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic,

acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, acetate, fumarate, citrate, tartrate, benzoate, p-toluenesulfonate, methanesulfonate or naphthalenesulfonate salt. Other non-pharmaceutically acceptable salts, eg. oxalates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention. The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

Certain groups, substituents, compounds or salts included in the present invention may be present as isomers. The present invention includes within its scope all such isomers, including racemates, enantiomers and mixtures thereof.

Certain of the groups, e.g. heteroaromatic ring systems, included in compounds of formula (I) or their salts may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

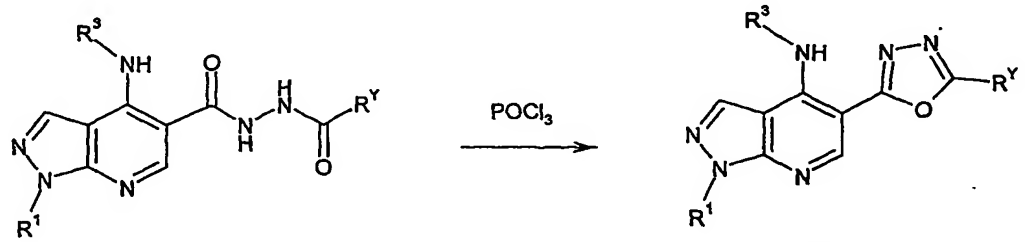
Especially when intended for oral medicinal use, the compound of formula (I) can optionally have a molecular weight of 1000 or less, for example 800 or less. Molecular weight here refers to that of the unsolvated "free base" compound, that is excluding any molecular weight contributed by any addition salts, solvent (e.g. water) molecules, etc.

Synthetic Process Routes

The following processes can be used to make the compounds of formula (I):

Process A

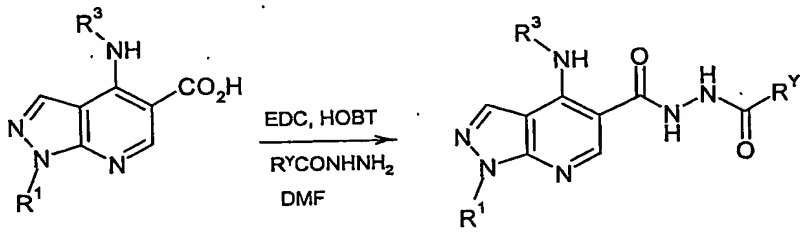
Compounds of Formula I can be prepared by the cyclisation reaction of a compound of Formula II, for example with phosphorous oxychloride, in a suitable solvent such as acetonitrile. The reaction may require heating:



Formula II

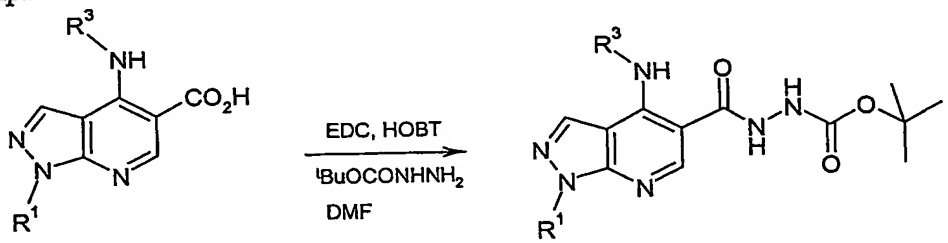
Formula I

Compounds of Formula II may themselves be prepared by reacting a compound of Formula III with a suitably substituted hydrazine derivative of formula $R^YCONHNH_2$, under standard coupling conditions. For example a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) may be used e.g. in the presence of hydroxybenzotriazole (HOBT) , for example in a suitable solvent such as DMF:

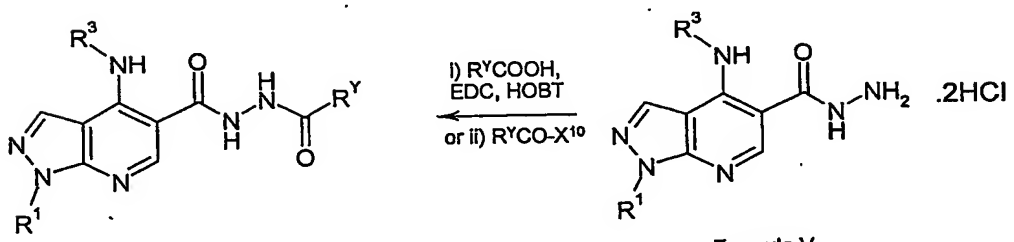


Formula III Formula II

Where the required hydrazine derivative $R^YCONHNH_2$ is not readily available, compounds of Formula II may alternatively be prepared by initially reacting a compound of Formula III with t-butylcarbazate under standard coupling conditions. For example a coupling reagent such as EDC may be used, e.g. in the presence of hydroxybenzotriazole, , for example in a suitable solvent such as DMF:



Formula III Formula IV

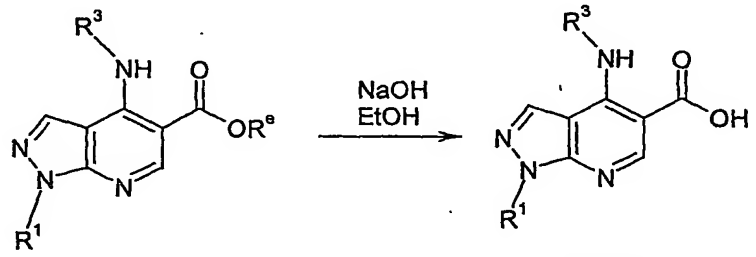


Formula II Formula V

Subsequent Boc-deprotection of the resultant acid hydrazide derivative (Formula IV) to afford a hydrazide derivative of Formula V, can be achieved using a dilute acid such as 2M hydrochloric acid in an organic solvent such as dioxane. Conversion to the desired hydrazide derivative of Formula II can be achieved by reaction with an acid of formula

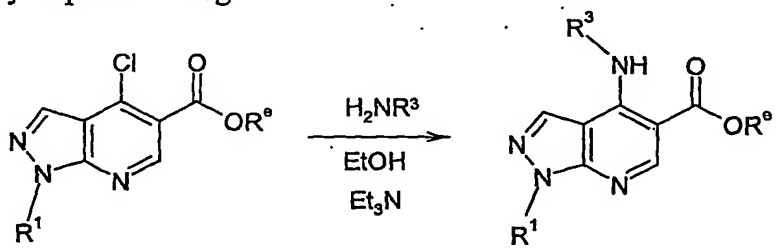
R^YCO_2H under standard coupling conditions. For example a coupling agent such as EDC may be used e.g. in the presence of hydroxybenzotriazole, for example in a suitable solvent such as DMF. Alternatively, an activated acid derivative of formula $R^YCO\text{-}X^{10}$ where X is a leaving group such as chloro (acid chloride) or -O-CO-R^{30} or -O-SO_2-R^{30} (where R^{30} can e.g. be R^Y or alkyl or aryl such as methyl, t-butyl or p-methylphenyl) may be used to effect formation of a hydrazide of Formula II, through reaction with a hydrazide derivative of Formula V.

Compounds of Formula III can be prepared by hydrolysis of an ester of Formula VI (for example R^e = Et), for example according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This hydrolysis procedure usually involves reaction with a base such as sodium hydroxide or potassium hydroxide in a solvent such as ethanol or dioxane, one or both solvents preferably containing some water:



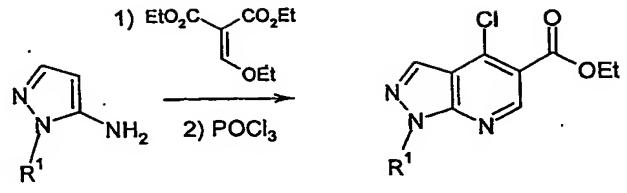
Formula VI Formula III

Compounds of Formula VI can be prepared, e.g. according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of Formula VII with an amine of Formula R^3NH_2. The reaction is best carried out in the presence of a base such as triethylamine or diisopropylethyl amine in a solvent such as ethanol or dioxane and may require heating:



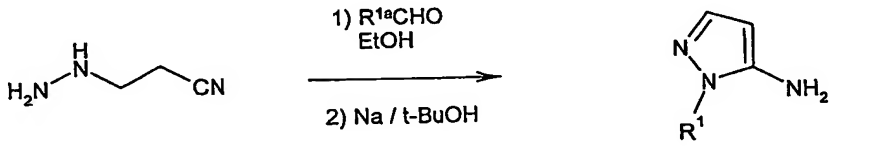
Formula VII Formula VI

Compounds of Formula VII are also described in the above reference and can be prepared first by reaction of a compound of Formula VIII with, for example, diethylethoxymethylene malonate (to afford R^e = Et) e.g. with heating, followed by reaction with phosphorous oxychloride, again with heating:



Formula VIII Formula VII

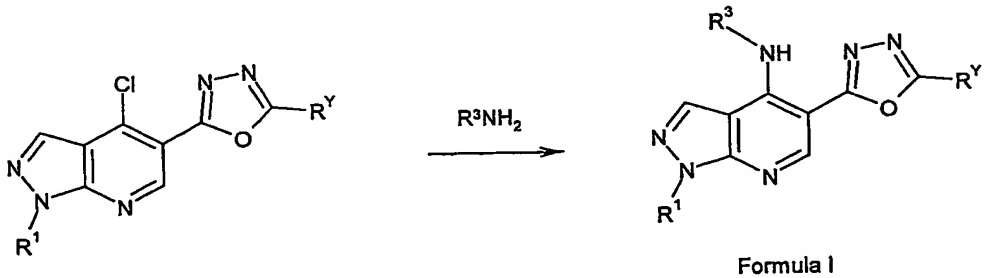
Where the desired amino pyrazole of Formula VIII is not commercially available, preparation can be achieved, for example using methods described by Dorgan et. al. in *J. Chem. Soc., Perkin Trans.* 1980, 1 (4), 938-42, involving reaction of cyanoethyl hydrazine with a suitable aldehyde $R^{1a}CHO$ in a solvent such as ethanol, with heating, followed by reduction with, for example sodium in a solvent such as t-butanol. R^{1a} should be chosen so as to contain one less carbon atom than R^1, for example R^{1a}= methyl will afford R^1 = ethyl.



Formula VIII

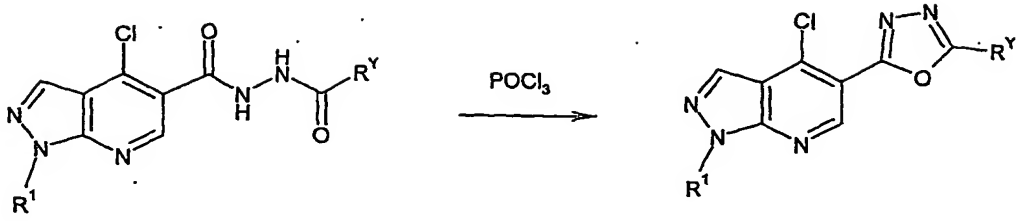
Process B

Compounds of Formula I can alternatively be prepared by reaction of a compound of Formula IX with an amine of formula R^3NH_2 , preferably in a solvent such as ethanol or acetonitrile, in the presence of a base such as DIPEA. Heating may be required to effect the conversion:



Formula IX Formula I

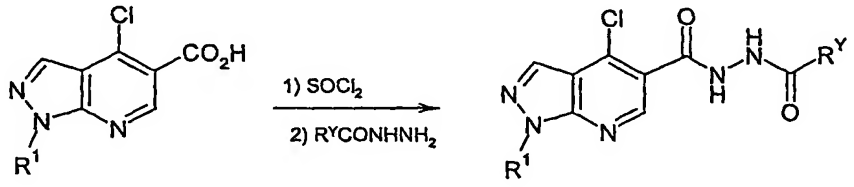
Compounds of Formula IX can themselves be prepared by reaction of a compound of Formula X with phosphorous oxychloride in a suitable solvent such as acetonitrile. The reaction may require heating:



Formula X

Formula IX

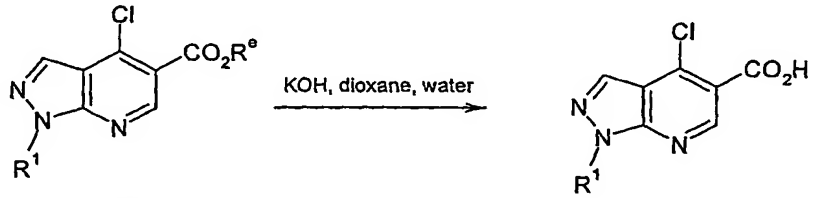
Compounds of Formula X can be prepared by initial reaction of an acid of Formula XI with standard amide coupling reagents such as EDC/HOBT or with thionyl chloride, followed by reaction of the thus formed activated intermediate with an acid hydrazide of Formula $R^YCONHNH_2$:



Formula XI

Formula X

Acids of Formula XI can themselves be prepared by hydrolysis of an ester of Formula VII using a base such as potassium hydroxide in a solvent such as aqueous dioxane.

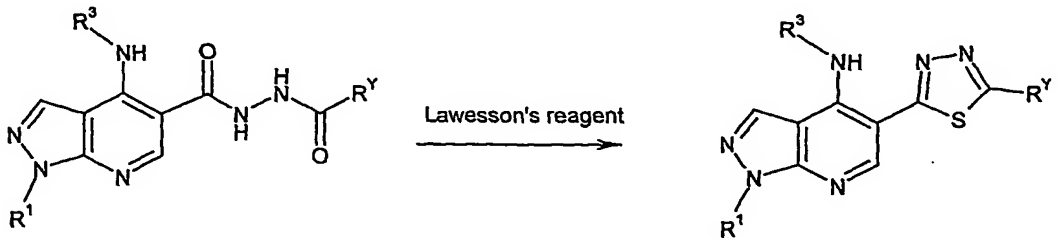


Formula VII

Formula XI

Process C

Compounds of Formula XII can be prepared by reaction of a compound of Formula II with a reagent capable of inserting sulfur such as Lawesson's reagent, usually in a suitable solvent such as acetonitrile. The reaction may require heating:

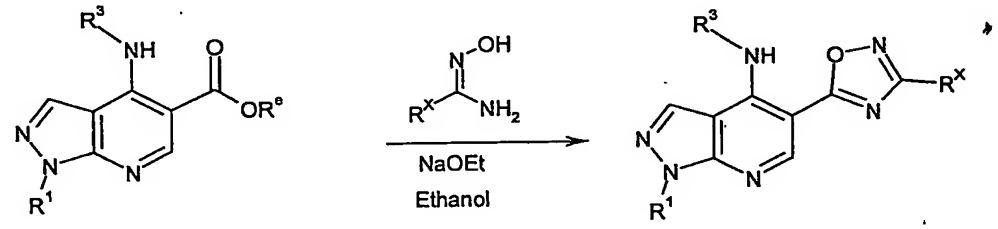


Formula II

Formula XII

Process D

Compounds of Formula XIII can be prepared by reaction of a compound of Formula VI (R^e = Et) with an amidoxime of formula $R^XC(NOH)NH_2$ and sodium ethoxide in the presence of molecular sieves and in a suitable solvent such as ethanol.

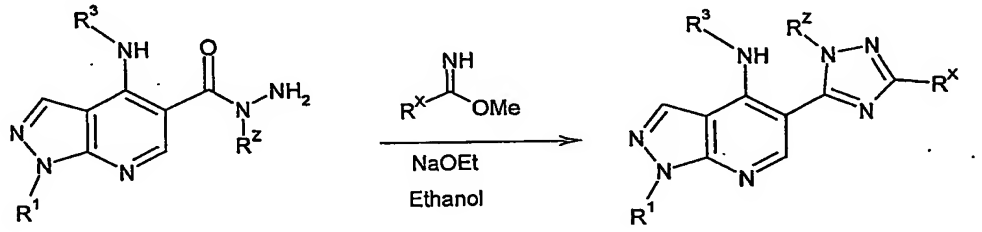


Formula VI

Formula XIII

Process E

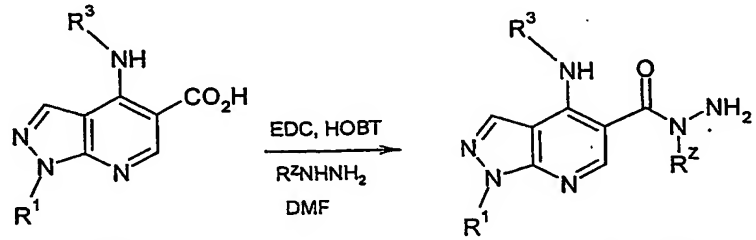
Compounds of Formula XIV can be prepared by reaction of a compound of Formula XV with a suitable acetimidate such as methyl acetimidate (R^X = Me) and triethylamine in a suitable solvent such as ethanol:



Formula XV

Formula XIV

Compounds of Formula XV may themselves be prepared by reaction of a compound of Formula III with a suitably substituted hydrazine derivative of Formula R^ZNHNH_2, under standard coupling conditions. For example a coupling agent such as EDC may be used in the presence of hydroxybenzotriazole, in a suitable solvent such as DMF:



Formula III

Formula XV

Process F

To make a compound of formula (I) wherein Het is optionally substituted 1,3-oxazol-2-yl, methods known to the skilled person can be used. For example, the 5-carboxylic acid of Formula (III) can be converted to a 5-(optionally-substituted 1,3-oxazol-2-yl)-pyrazolopyridine by the method shown in Example 41 or a modification of this method or by an analogous method.

The present invention therefore also provides a method of preparing a compound of formula (I) or a salt thereof, comprising :

(a) cyclisation of a compound of formula (II) to an optionally substituted 1,3,4-oxadiazol-2-yl derivative at the 5-position of the pyrazolopyridine ring system, for example in the presence of phosphorus oxychloride, or

(b) reaction of a compound of formula (IX) with an amine of formula R^3NH_2, or

(c) cyclisation of a compound of formula (II) to an optionally substituted 1,3,4-thiadiazol-2-yl derivative at the 5-position of the pyrazolopyridine ring system, for example in the presence of an agent cpable of introducing sulfur such as Lawesson's reagent, or

(d) reaction of a compound of formula (VI), with an amidoxime of formula $R^XC(NOH)NH_2$ or a salt thereof; or

(e) reaction of a compound of formula (XV) to an optionally substituted 1,2,4-triazol- 3-yl or 5-yl derivative at the 5-position of the pyrazolopyridine ring system

and optionally converting the compound of formula (I) into a salt e.g. a pharmaceutically acceptable salt.

Medical uses

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the conditions described herein and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic bronchitis, emphysema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, or multiple sclerosis.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD), asthma, or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human). PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein) and COPD (e.g. see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (SL Wolda, 2000).

Pharmaceutical compositions and dosing

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. Accordingly , the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for inhaled or oral administration, e.g. to a mammal such as a

human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition. Oral administration to a human is most preferred.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. Examples of such carriers include lactose and cellulose. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example binding agents, lubricants such as magnesium stearate, and/or tablet disintegrants.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-

heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Preferably, a pharmaceutical composition for inhaled administration is incorporated into a plurality of sealed dose containers mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable on demand and the dose administered by inhalation via the device such as the DISKUS TM device, marketed by GlaxoSmithKline.

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration.

In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.01 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

Combinations

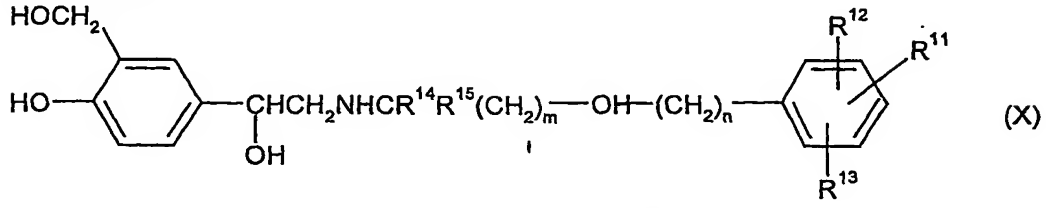
The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with another therapeutically active agent, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic or an anti-inflammatory agent.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another therapeutically active agent, for example, a β_2-adrenoreceptor agonist, an anti-histamine, an anti-allergic, an anti-inflammatory agent or an antiinfective agent.

Examples of β_2-adrenoreceptor agonists include salmeterol (eg as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Preferred long acting β_2-adrenoreceptor agonists include those described in WO 02/66422A.

Especially preferred long-acting β_2-adrenoreceptor agonists include compounds of formula(X):



(X)

or a salt or solvate thereof, wherein in formula (X):
m is an integer of from 2 to 8;
n is an integer of from 3 to 11,
with the proviso that m + n is 5 to 19,
R^{11} is $-XSO_2NR^{16}R^{17}$ wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;
R^{16} and R^{17} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{18}R^{19}$, phenyl, and phenyl (C_{1-4}alkyl)-,
or R^{16} and R^{17}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^{16} and R^{17} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{18}$, $-SO_2NR^{18}R^{19}$, $-CONR^{18}R^{19}$, $-NR^{18}C(O)R^{19}$, or a 5-, 6- or 7-membered heterocylic ring;
R^{18} and R^{19} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and
p is an integer of from 0 to 6, preferably from 0 to 4;
R^{12} and R^{13} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and
R^{14} and R^{15} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{14} and R^{15} is not more than 4.

Examples of anti-histamines include methapyrilene or loratadine.

Other suitable combinations include, for example, other anti-inflammatory agents eg. NSAIDs (eg. leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or antiinfective agents (eg. antibiotics, antivirals).

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical composition.

Biological Test Methods

PDE 3, PDE 4B, PDE 5 Primary assay methods

The activity of the compounds can be measured in the assay methods shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5.

Human recombinant PDE4B

Human recombinant PDE4B is disclosed in WO 94/20079 and also M.M. McLaughlin et al., A low *Km*, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA, *J. Biol. Chem.*, 1993, **268**, 6470-6476). Human recombinant PDE4B was expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62. 100,000 x *g* supernatant fractions of yeast cell lysates were used for PDE4B assays and inhibitor studies.

Inhibition of PDE 3, PDE 4B, or PDE 5 activity

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant), PDE3 (from bovine aorta) or PDE5 (human recombinant) was determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds were preincubated at ambient temperature in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes. The enzyme concentration was adjusted so that no more than 20% hydrolysis of the substrate occurred in control wells without compound, during the incubation. For PDE3 and PDE4B assay [5',8-^{3}H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.559) was added to give 0.05uCi per well and ~ 10nM final concentration. For PDE5 assay [8-^{3}H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.392) was added to give 0.05uCi per well and ~ 36nM final concentration. Plates were mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) were added (~1mg per well) to terminate the assay. Plates were sealed and shaken and allowed to stand at ambient temperature for 1hour to allow the beads to settle. Bound radioactive product was measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound were assayed. Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited) Results were expressed as pIC_{50} values.

Biological Data obtained for some of the Examples (PDE4B inhibitory activity, either as one reading or as an avarage of ca. 2-6 readings) are as follows. Absolute accuracy is not possible, and the readings given are accurate only up to about ± 0.5 of a log unit:

Example	PDE4B pIC_{50}
6	8.1
10	8.2
12	7.9
14	7.6
23	8.2
24	8.2

Most or all of the examples have PDE4B inhibitory activities in the range of pIC_{50} = ca. 5.5 to ca. 8.5 (± 0.5), more usually ca. 6 to ca. 8.5 (± 0.5) or ca. 6.7 to ca. 8.4 (± 0.5).

Emesis: Many known PDE4 inhibitors cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable but not essential if a particular PDE4 inhibitory compound of the invention were to cause only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting, retching and/or writhing in ferrets after oral or parenteral administration of the compound. See for example A. Robichaud et al., "Emesis induced by inhibitors of [PDE IV] in the ferret", *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465.

Other side effects: Many known PDE4 inhibitors cause other side effects such as headache and other central nervous sytem (CNS-) mediated side effects; and/or gastrointestinal (GI) tract disturbances. Therefore, it would be preferable but not essential if a particular PDE4 inhibitory compound of the invention were to cause only limited or manageable side-effects in one or more of these side-effect categories.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

BEMP	2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphazine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMF	dimethyl formamide
EtOAc	ethyl acetate
Et_2O	diethyl ether
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBT	hydroxybenzotriazole
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HPLC	High performance liquid chromatography
LCMS	liquid chromatography / mass spectroscopy
MeCN	acetonitrile
MeOH	methanol
NMR	nuclear magnetic resonance
DIPEA	N,N-diisopropylethylamine
SPE	solid phase extraction
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
THF	Tetrahydrofuran
T_{RET}	retention time
TLC	thin layer chromatography
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide
Burgess Reagent	(Methoxycarbonylsulphamoyl)triethylammonium hydroxide

Machine Methods used herein:

LCMS (liquid chromatography / mass spectroscopy)
Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM

Column : 3.3cm x 4.6mm ID, 3µm ABZ+PLUS
Flow Rate : 3ml/min
Injection Volume : 5µl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min

Mass directed autoprep HPLC
The prep column used was a Supelcosil ABZplus (10cm x 2.12cm)
UV wavelength : 200-320nM
Flow : 20ml/min
Injection Volume: 1ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 5% formic acid
Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-100%A/0.1min

Microwave
The CEM Discover Focused Microwave Synthesis system was used.

Intermediates and Examples

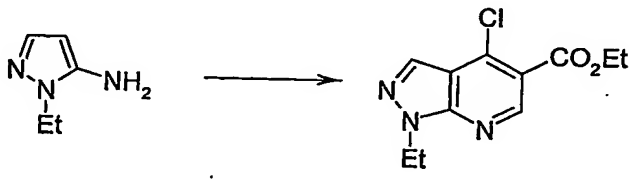
All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich.

Table of Intermediates

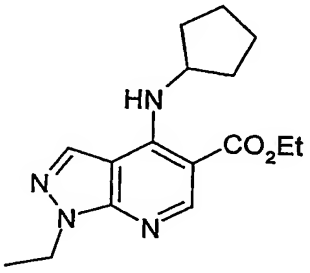
Intermediate Number	Name
1	Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
3	4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
4	N'-Acetyl-4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
5	4-(Cyclopentylamino)-1-ethyl-N'-[(methylsulfonyl)acetyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
6	Ethyl 4-(4-fluorophenylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
7	4-(Cyclopentylamino)-1-ethyl-N-[methyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
8	Methanesulfonyl acetic acid hydrazide
9	Acetamidoxime

10	4-(Cyclopentylamino)-1-ethyl-N'-isobutyryl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
11	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
12	4-Chloro-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine
13	4-Chloro-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine
14	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine
15	4-Chloro-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridine
16	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
17	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
18	Tert-butyl 2-{[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]carbonyl}hydrazinecarboxylate
19	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide dihydrochloride
20	N'-(Cyclopropylcarbonyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
21	Tetrahydro-2H-pyran-4-amine = 4-Aminotetrahydropyran
21A	Tetrahydro-2H-pyran-4-amine hydrochloride = 4-aminotetrahydropyran hydrochloride
22	N'-Hydroxy-2-methoxyethanimidamide
23	2-(Dimethylamino)-N'-hydroxyethanimidamide
24	N'-Hydroxy-2-morpholin-4-ylethanimidamide
25	1-Acetyl-4-aminopiperidine hydrochloride
26	3-Methyloxetane-3-carboxylic acid
27	(4-Methylpiperazin-1-yl)acetic acid
28	(Isopropylamino)(oxo)acetic acid
29	1-Methyl-5-oxopyrrolidine-3-carboxylic acid
30	Tetrahydro-2H-pyran-4-carboxylic acid
31	Morpholin-4-ylacetic acid
32	Tert-butoxyacetic acid

Intermediate 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
Prepared from commercially available 5-amino-1-ethyl pyrazole as described by G. Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027:

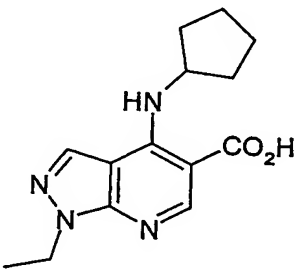


Intermediate 2: Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Intermediate 1 (0.051g) and cyclopentyl amine (0.019g) were suspended in ethanol (2ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM and water. The organic layer was loaded directly onto an SPE cartridge (silica, 5g) and eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O, (v) EtOAc and (vi) MeOH. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 2 (0.074g). LCMS showed $MH^+ = 303$; $T_{RET} = 3.45$min

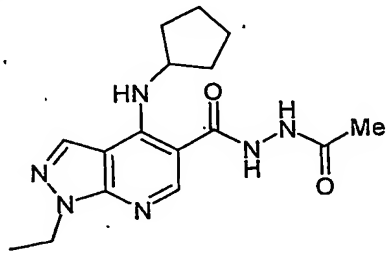
Intermediate 3: 4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 2 (2.2g) in ethanol: water (95:5, 16.85ml) was treated with sodium hydroxide (1.2g) and heated at 50°C for 16h. The mixture was concentrated in vacuo and the residue re-dissolved in water (0.85ml). The solution was acidified to pH4

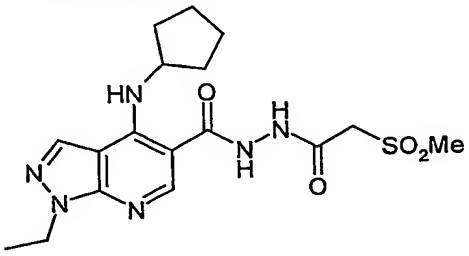
using acetic acid and the resultant white precipitate was collected by filtration and dried under vacuum to afford Intermediate 3 (1.9g). LCMS showed MH^+ = 275; T_{RET} = 2.65min

Intermediate 4: N'-Acetyl-4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



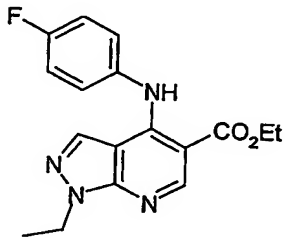
Intermediate 3 (0.066g), EDC (0.06g) and HOBT (0.035g) were suspended in DMF (2ml) and the mixture was stirred for 15 minutes. Acetic hydrazide (0.02g) was then added and the mixture stirred under nitrogen for 18h. Solvents were removed by concentration in vacuo and the residue partitioned between DCM and water. The layers were separated and the organic phase was washed with saturated aqueous sodium bicarbonate solution, then concentrated and applied to an SPE cartridge (aminopropyl, 1g) which was eluted with methanol. Concentration in vacuo afforded Intermediate 4 (0.043g). LCMS showed MH^+ = 331; T_{RET} = 2.38min.

Intermediate 5: 4-(Cyclopentylamino)-1-ethyl-N'-[(methylsulfonyl)acetyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



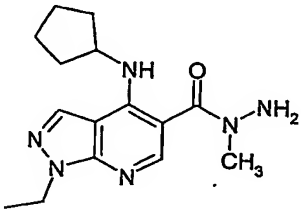
Intermediate 3 (0.12g), EDC (0.12g) and HOBT (0.072g) were suspended in DMF (2ml) and stirred for 15 minutes. Intermediate 8 (0.082g) was then added and the mixture stirred under nitrogen for 18h. Reaction was incomplete so a further portion of Intermediate 8 was added (0.040g) and stirring continued for a further 66h. Solvents were removed in vacuo and the residue partitioned between DCM and water. The aqueous phase was further extracted with DCM and the combined organic layers applied to an SPE cartridge (silica, 5g) which was eluted sequentially with a gradient of Et_2O: MeOH (1:0, 9:1, 8:2, 7:3 and 6:4). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 5 (0.154g). LCMS showed MH^+ = 409; T_{RET} = 2.42min.

Intermediate 6: Ethyl 4-(4-fluorophenylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Intermediate 1 (0.051g) and 4-fluoroaniline (0.024g) were suspended in ethanol (2ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM and water. The organic layer was loaded directly onto an SPE cartridge (silica, 5g) and eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O, (v) EtOAc, (vi) MeOH. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 6 (0.077g). LCMS showed $MH^+ = 328$; $T_{RET} = 3.36$min.

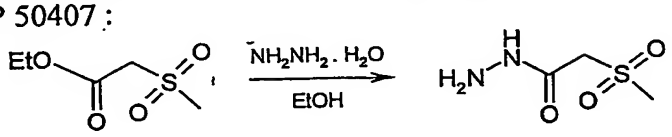
Intermediate 7: 4-(Cyclopentylamino)-1-ethyl-N-[methyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



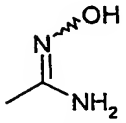
Intermediate 3 (0.10g) was dissolved in DMF (2ml) and treated with HBTU (0.136g) and DIPEA (0.116g). A separate portion of Intermediate 3 (0.10g) was dissolved in DMF (2ml) and treated with EDC (0.096g) and HOBT (0.058g). The resultant suspensions were both stirred under nitrogen for 15min, then methyl hydrazine (0.017g) added to each and stirring continued under nitrogen for 18h. The mixtures were independently concentrated in vacuo and the residues partitioned between DCM and water. The organic layers were concentrated and each applied to an SPE cartridge (aminopropyl, 2g) which was eluted with methanol, followed by 10% ammonia in methanol. The two portions of Intermediate 7 thus afforded were combined (0.16g). LCMS showed $MH^+ = 303$; $T_{RET} = 2.22$min.

Intermediate 8: Methanesulfonyl acetic acid hydrazide

Prepared from commercially available ethyl methylsulphonyl acetate as described by D. E. Bays et. al. in EP 50407 :

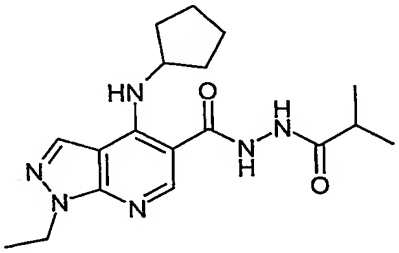


Intermediate 9: Acetamidoxime



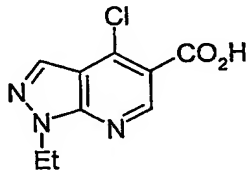
Can be prepared from aqueous hydroxylamine and acetonitrile as described by J. J. Sahbari et. al. in WO 00032565.

Intermediate 10: 4-(Cyclopentylamino)-1-ethyl-N'-isobutyryl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



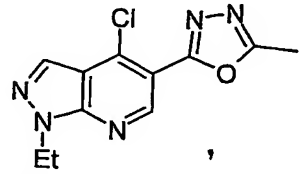
Intermediate 3 (0.060g), EDC (0.06g) and HOBT (0.035g) were suspended in DMF (2ml) and stirred under nitrogen for 15 minutes. Isobutyric acid hydrazide (0.027g) was then added and the mixture stirred under nitrogen for 18h. Solvents were removed in vacuo and the residue partitioned between DCM and water. The organic phase was washed with saturated aqueous sodium bicarbonate solution, then concentrated in vacuo and applied to an SPE cartridge (aminopropyl, 1g) which was eluted with methanol. Concentration in vacuo afforded Intermediate 10. LCMS showed $MH^+ = 359$; $T_{RET} = 2.70$min.

Intermediate 11: 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



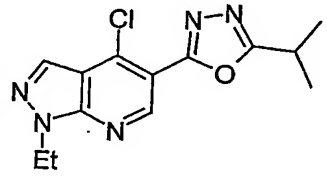
A solution of Intermediate 1 (3.5g) in dioxane (28ml) was treated with potassium hydroxide (6.3g) as a solution in water (20ml). The mixture was stirred for 2h, then concentrated in vacuo, acidified to pH 3 with 2M aqueous hydrochloric acid and extracted with ethyl acetate. The layers were separated, the organic layer dried over sodium sulphate, then concentrated in vacuo to afford Intermediate 11 as a white solid (2.4g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.62$min.

Intermediate 12: 4-Chloro-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine



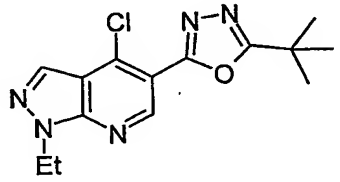
Intermediate 11 (0.4g) was dissolved in thionyl chloride (3ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (2ml). This solution was added to a solution of acetic hydrazide (0.145g) and diisopropylethylamine (0.465ml) in anhydrous acetonitrile (2ml), and the mixture stirred for a further 2h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (4ml). The resultant solution was stirred and heated at reflux (120°C) for 0.5h, then allowed to cool and purified by Biotage (silica, 40g), eluting with cyclohexane : EtOAc (1:1) to afford Intermediate 12 (0.32g). LCMS showed $MH^+ = 264$; $T_{RET} = 2.55$ min.

Intermediate 13: 4-Chloro-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine



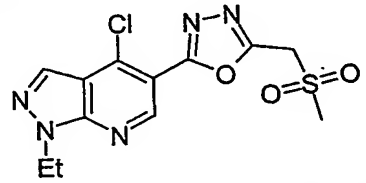
Intermediate 11 (0.05g) was dissolved in thionyl chloride (1ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (0.5ml). This solution was added to a solution of isobutyric acid hydrazide (0.025g) and diisopropylethylamine (0.058ml) in anhydrous acetonitrile (1ml), and the mixture stirred for a further 1.5h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (2ml). The resultant solution was stirred and heated at reflux (120°C) for 2h, then allowed to cool and concentrated in vacuo. The residue was applied to an SPE cartridge (silica, 5g) which was eluted sequentially with a gradient of EtOAc : cyclohexane (i) 1:16, (ii) 1:8, (iii) 1:4, (iv) 1:2, (v) 1:1 and (vi) 1:0. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 13 (0.049g). LCMS showed $MH^+ = 292$; $T_{RET} = 2.96$min.

Intermediate 14: 5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine



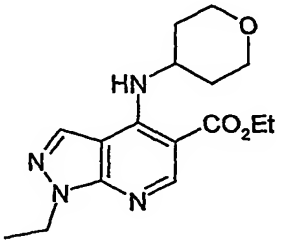
Intermediate 11 (0.40g) was dissolved in thionyl chloride (3ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (2ml). This solution was added to a solution of pivalic acid hydrazide (0.228g) and diisopropylethylamine (0.465ml) in anhydrous acetonitrile (2ml), and the mixture stirred for a further 1.5h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (5ml). The resultant solution was stirred and heated at reflux (120°C) for 1.5h, then allowed to cool, concentrated in vacuo and purified by Biotage (silica, 40g), eluting with petroleum ether (40/60) : EtOAc (1:1) to afford Intermediate 14 (0.388g). LCMS showed MH^+ = 306; T_{RET} = 3.14 min.

Intermediate 15: 4-Chloro-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridine



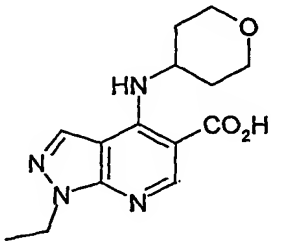
Intermediate 11 (0.68g) was dissolved in thionyl chloride (4ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (3ml). This solution was added dropwise over 5 minutes to a solution of Intermediate 8 (0.504g) and diisopropylethylamine (0.787ml) in anhydrous acetonitrile (12ml), and the mixture then stirred for a further 1h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (8ml). The resultant solution was stirred and heated at reflux (120°C) for 2.5h, then allowed to cool, concentrated in vacuo and purified by Biotage (silica, 40g), eluting first with petroleum ether (40/60) : EtOAc (2:1), then with petroleum ether (40/60) : EtOAc (1:1). Fractions containing desired material were combined, concentrated in vacuo and the residue further purified by trituration with diethyl ether to afford Intermediate 15 (0.41g). LCMS showed MH^+ = 342; T_{RET} = 2.46 min.

Intermediate 16: Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



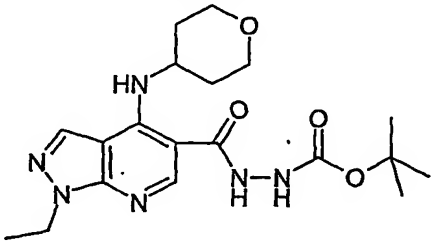
Intermediate 1 (0.20g) and triethylamine (0.55ml) were suspended in ethanol (8ml) and 4-aminotetrahydropyran (Intermediate 21, 0.088g) was added. The mixture was stirred under nitrogen, heated at 80°C for 16h, then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was loaded directly onto an SPE cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O and (v) EtOAc. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 16 (0.21g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.93$min.

Intermediate 17: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 16 (0.21g) in ethanol : water (95:5, 10ml) was treated with sodium hydroxide (0.12g). The mixture was heated at 50°C for 8h, then concentrated in vacuo, dissolved in water and acidified to pH 4 with acetic acid. The resultant white solid was removed by filtration and dried under vacuum to afford Intermediate 17 as an off-white solid (0.16g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.11$min.

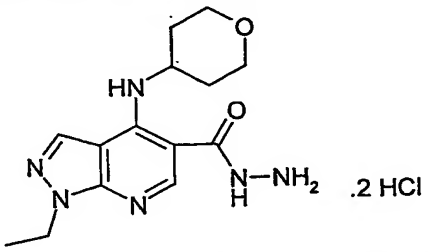
Intermediate 18: Tert-butyl 2-{[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]carbonyl}hydrazinecarboxylate



A suspension of Intermediate 17 (1.48g), EDC (1.34g) and HOBT (0.83g) in DMF (20ml) was stirred at room temperature for 30min. t-Butyl carbazate (0.68g) was then

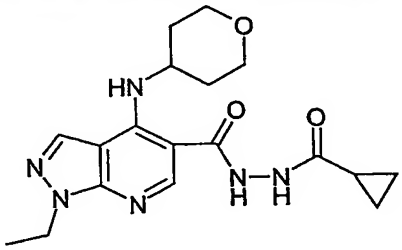
added and stirring continued under nitrogen for a further 66h. The mixture was concentrated in vacuo and the residue divided into two portions for purification. Each portion was applied to an SPE cartridge (aminopropyl, 10g) which was eluted with methanol and the combined eluents were concentrated in vacuo. Further purification was carried out by Biotage (silica, 40g), eluting with cyclohexane : ethyl acetate (1:4). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 18 (1.39g). LCMS showed $MH^+ = 405$; $T_{RET} = 2.64$min.

Intermediate 19: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide dihydrochloride



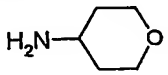
Intermediate 18 (1.39g) was treated with a 4M solution of hydrochloric acid in dioxane (8ml) and the mixture stirred under nitrogen for 1h. Concentration in vacuo afforded Intermediate 19 as a white solid (1.17g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.04$min.

Intermediate 20: N'-(Cyclopropylcarbonyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



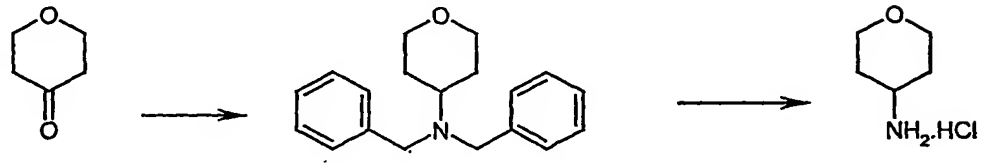
A solution of Intermediate 19 (0.045g) in THF (2ml) was treated with DIPEA (0.045ml), then with cyclopropylcarbonyl chloride (0.013g) and stirred at room temperature for 16h. The mixture was concentrated in vacuo and the residue partitioned between dichloromethane and water. The layers were separated and the organic layer concentrated in vacuo, then applied to an SPE cartridge (aminopropyl, 1g). The column was eluted with methanol to afford Intermediate 20 as a white solid (0.02g). LCMS showed $MH^+ = 373$; $T_{RET} = 2.15$min.

Intermediate 21: 4-Aminotetrahydropyran



Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126 (CAS 38041-19-9)

Intermediate 21A: **Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride**



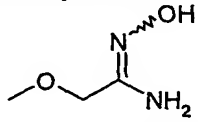
Step1: N,N-dibenzyltetrahydro-2H-pyran-4-amine

Dibenzylamine (34.5g) and acetic acid (6.7ml) were added to a stirred solution of tetrahydro-4H-pyran-4-one (16.4g, commercially available from e.g. Aldrich) in dichloromethane (260ml) at 0 °C to 5 °C. After 2.5h at 0 °C to 5 °C, sodium triacetoxyborohydride (38.9g) was added portionwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction mixture was washed successively with 2M-sodium hydroxide (200ml and 50ml), water (2 x 50ml) and brine (50ml), then dried and evaporated to give a yellow oil (45g). This oil was stirred with methanol (50ml) at 4 °C for 30min to give the product as a white solid (21.5g). LCMS showed $MH^+ = 282$; $T_{RET} = 1.98$ min.

Step 2: Tetrahydro-2H-pyran-4-amine hydrochloride

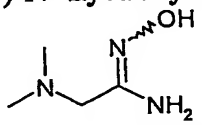
N,N-dibenzyltetrahydro-2*H*-pyran-4-amine (20.5g) was dissolved in ethanol (210ml) and hydrogenated over 10% palladium on carbon catalyst (4g) at 100 psi for 72h at room temperature. The reaction mixture was filtered and the filtrate was adjusted to pH 1 with 2M-hydrogen chloride in diethyl ether. Evaporation of solvents gave a solid which was triturated with diethyl ether to give the product as a white solid (9.23g). ^{1}H NMR (400MHz, d_6-DMSO, δppm) 8.24 (br. s, 3H), 3.86 (dd, 12, 4Hz, 2H), 3.31 (dt, 2, 12Hz, 2H), 3.20 (m, 1H), 1.84 (m, 2H), 1.55 (dq, 4, 12Hz, 2H).

Intermediate 22: **N'-Hydroxy-2-methoxyethanimidamide**



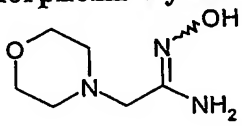
A solution of methoxyacetonitrile (12.26g) in ethanol (220ml) was treated with hydroxylamine hydrochloride (11.95g) followed by potassium carbonate (22.9g) and heated under reflux for 2 days. The mixture was concentrated in vacuo, then partitioned between ethylacetate and water. The organic layer was concentrated in vacuo to afford Intermediate 22 as a colourless liquid (7.6g). ^{1}H NMR ($CDCl_3$) 7.16 (3H, s), 7.67 (s, 2H), 9.32 (brs, 2H), 13.08 (1H, s).

Intermediate 23: 2-(Dimethylamino)-N'-hydroxyethanimidamide



Can be prepared in an analogous manner to Intermediate 9, starting from dimethylamino acetonitrile.

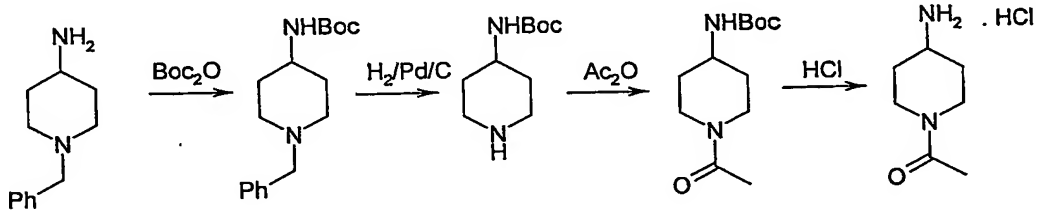
Intermediate 24: N'-Hydroxy-2-morpholin-4-ylethanimidamide



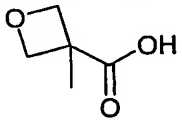
Can be prepared in an analogous manner to Intermediate 9, starting from morpholino acetonitrile (itself commercially available from TCI America, 9211 North Harborgate Street, Portland, OR 97203, USA).

Intermediate 25: 1-Acetyl-4-aminopiperidine hydrochloride

Prepared from commercially available N1-benzyl-4-aminopiperidine as described by Yamada *et. al.* In WO 00/42011:

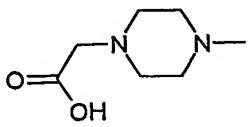


Intermediate 26: 3-Methyloxetane-3-carboxylic acid



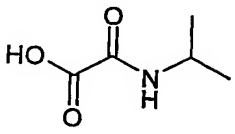
Can be prepared by oxidation of 3-Methyl-3-oxetanemethanol (commercially available from e.g. Fluka, CAS 3143-02-0) according to the procedure described by H. Fiege *et. al.* in DE3618142.

Intermediate 27: (4-Methylpiperazin-1-yl)acetic acid



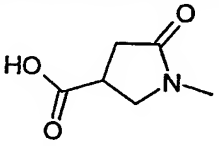
Commercially available from ChemPacific USA Sales Marketing and Research Center, 6200 Freeport Centre, Baltimore, MD 21224, USA (CAS 54699-92-2).

Intermediate 28: (Isopropylamino)(oxo)acetic acid



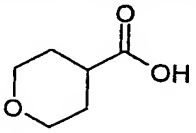
Commercially available from Austin Chemical Company, Inc., 1565 Barclay Blvd., Buffalo Grove, IL 60089, USA (CAS 3338-22-5)

Intermediate 29: 1-Methyl-5-oxopyrrolidine-3-carboxylic acid



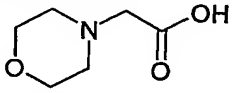
Commercially available from MicroChemistry-RadaPharma, Shosse Entusiastov 56, Moscow 111123, Russia (CAS 42346-68-9).

Intermediate 30: Tetrahydro-2H-pyran-4-carboxylic acid



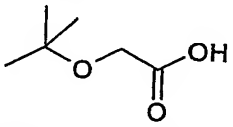
Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA (CAS 5337-03-1)

Intermediate 31: Morpholin-4-ylacetic acid



Can be prepared from ethyl bromoacetate as described by Z. Dega-Szafran et. al. in *J. Molecular Structure*, 2001, 560, 261-273.

Intermediate 32: Tert-butoxyacetic acid



A suspension of sodium t-butoxide (24.1g) in t-butanol (150ml) was cooled in a water bath and treated drop-wise with a solution of chloroacetic acid (11.4g) in t-butanol (30ml). The mixture was heated under reflux for 5h then concentrated in vacuo. The resultant white solid was dried in vacuo for 16h then water (100ml) was added and the mixture was filtered. The filtrate was treated with diethyl ether (150ml), then cooled in an ice bath, stirred and acidified to pH1 with 2N sulphuric acid. The layers were separated and the aqueous layer was further extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford Intermediate 32 (11.1g). ^1H NMR (400MHz, $CDCl_3$, δppm) 1.27 (9H, s), 4.04 (2H, s).

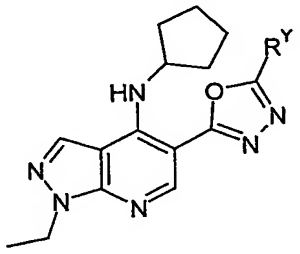
Table of Examples

Example Number	Name
1	N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
2	N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
3	N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
4	N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
5	N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
6	N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
7	1-Ethyl-N-(4-fluorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
8	N-Cyclopentyl-5-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
9	1-Ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
10	N-Cyclohexyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
11	1-Ethyl-N-isobutyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
12	1-Ethyl-N-isobutyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
13	N-Cyclohexyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
14	1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
15	N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
16	N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
17	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
18	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclohexyl-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
19	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-

	b]pyridin-4-amine
20	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-isobutyl-1H-pyrazolo[3,4-b]pyridin-4-amine
21	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1S)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
22	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1R)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
23	1-Ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
24	N-Cyclohexyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
25	1-Ethyl-N-isobutyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
26	N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
27	N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
28	1-Ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
29	1-Ethyl-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
30	5-{3-[(Dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
31	1-Ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
32	5-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
33	N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
34	1-Ethyl-5-[5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
35	1-Ethyl-5-{5-[(4-methylpiperazin-1-yl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
36	5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-isopropyl-1,3,4-oxadiazole-2-carboxamide
37	4-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-1-methylpyrrolidin-2-one
38	1-Ethyl-N-tetrahydro-2H-pyran-4-yl-5-(5-tetrahydro-2H-pyran-4-yl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
39	1-Ethyl-5-[5-(morpholin-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
40	5-[5-(Tert-butoxymethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine

41	**Methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3-oxazole-4-carboxylate**

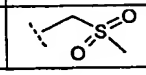
Example 1: N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



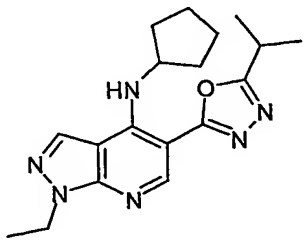
Example 1 R^Y = Me

Intermediate 4 (0.043g) was dissolved in acetonitrile (2ml) then treated with phosphorous oxychloride (0.101g) and stirred under nitrogen and heated at 90°C for 2h. The mixture was concentrated in vacuo and the residue partitioned between DCM and saturated aqueous sodium bicarbonate solution. The organic layer was concentrated in vacuo and applied to an SPE cartridge (aminopropyl, 1g), which was eluted with methanol. Concentration in vacuo afforded Example 1 (0.032g). LCMS showed $MH^+ = 313$; $T_{RET} = 3.13$min.

Similarly prepared but with an extended reaction time (see table) was:

	R^Y	Starting material	Reaction time	MH^+ ion	T_{RET}(min)
Example 2		Intermediate 5	3h	391	2.88

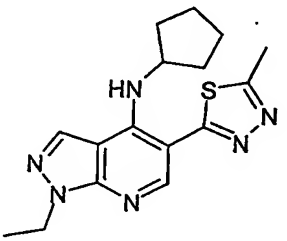
Example 3: N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 10 was dissolved in acetonitrile (2ml) then treated with phosphorous oxychloride (0.101g) and stirred under nitrogen at 90°C for 3.5h. The mixture was concentrated in vacuo and the residue partitioned between DCM and saturated aqueous

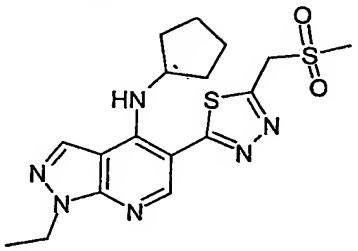
sodium bicarbonate solution. The organic layer was concentrated in vacuo and the residue applied to a SPE cartridge (silica, 5g), which was eluted with cyclohexane : Et_2O (1:2). Fractions containing desired material were combined and concentrated in vacuo to afford Example 3 (0.034g). LCMS showed $MH^+ = 341$; $T_{RET} = 3.39$min.

Example 4: N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



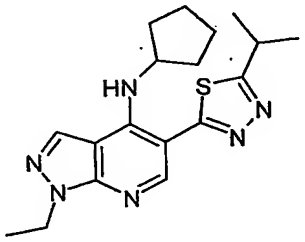
A solution of Intermediate 4 (0.09g) in acetonitrile (5ml) was stirred under nitrogen and treated with Lawesson's reagent (0.116g). The mixture was heated at 65°C for 16h, then concentrated in vacuo. The residue was applied to an SPE cartridge (silica, 5g) and eluted with a gradient of cyclohexane : Et_2O (1:2 then 1:3, 1:4, 1:5, 0:1). Fractions containing desired material were combined and concentrated in vacuo. Further purification was achieved using mass directed autoprep HPLC to afford Example 4 (0.002g). LCMS showed $MH^+ = 339$; $T_{RET} = 3.23$min.

Example 5: N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine



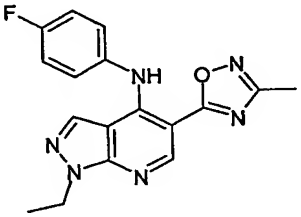
A solution of Intermediate 5 (0.07g) in acetonitrile (3ml) was stirred under nitrogen and treated with Lawesson's reagent (0.085g). The mixture was heated at 65°C for 136h, then concentrated in vacuo. The residue was partitioned between DCM and water and the organic layer concentrated in vacuo. Further purification was achieved using mass directed autoprep HPLC to afford Example 5 (0.008g). LCMS showed $MH^+ = 407$; $T_{RET} = 2.98$min.

Example 6: N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



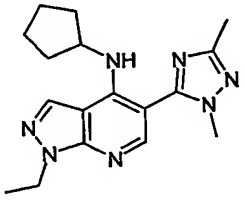
Intermediate 10 was dissolved in acetonitrile (5ml) then treated with Lawesson's reagent (0.125g) and heated under nitrogen at 65°C for 66h. Volatiles were removed in vacuo and the residue was purified by mass directed autoprep HPLC to afford Example 6. LCMS showed $MH^+ = 357$; $T_{RET} = 3.59$min.

Example 7: 1-Ethyl-N-(4-fluorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Intermediate 6 (0.04g) in ethanol (1ml) was stirred over powdered 4Å molecular sieves (0.290g) and treated with Intermediate 9 (0.045g), followed by sodium ethoxide (0.020g). The mixture was heated under reflux for 18h, then cooled and filtered. Following concentration of the filtrate in vacuo, the residue was applied to an SPE cartridge (silica, 5g) which was eluted with cyclohexane : Et_2O (1:1). Fractions containing desired material were combined and concentrated in vacuo to afford Example 7 (0.017g). LCMS showed $MH^+ = 339$; $T_{RET} = 3.23$min.

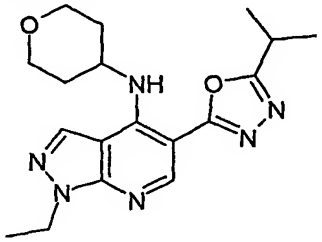
Example 8: N-Cyclopentyl-5-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Intermediate 7 (0.06g) in ethanol (2ml) was treated with triethylamine (0.101g), followed by methyl acetimidate hydrochloride (0.033g) and the mixture heated under reflux (80°C) for 42h. Reaction was incomplete so a further portion of methyl acetimidate hydrochloride (0.033g) was added and stirring continued under reflux for 6 days. The mixture was concentrated in vacuo and the residue partitioned between DCM

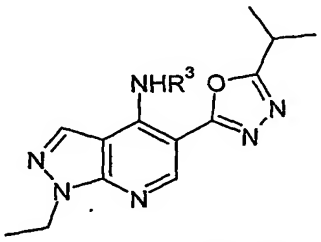
and 2M aqueous HCl. The organic layer was concentrated in vacuo and purified by mass directed autoprep to afford Example 8 (0.003g). LCMS showed MH^+ = 326; T_{RET} = 2.66min.

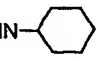
Example 9: 1-Ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 13 (0.016g) was dissolved in anhydrous acetonitrile (1ml). 4-Aminotetrahydropyran hydrochloride (Intermediate 21A, 0.008g) was then added, followed by diisopropylethyl amine (0.05ml) and the mixture was stirred under nitrogen at 75°C for 19h. A further portion of 4-aminotetrahydropyran (0.002g) was added and stirring continued at 85°C for 16h. The mixture was concentrated in vacuo and partitioned between DCM and water. The organic phase was concentrated in vacuo and applied to an SPE cartridge (silica, 1g), which was eluted sequentially with a gradient of EtOAc: cyclohexane (i) 1:8, (ii) 1:4, (iii) 1:2, (iv) 1:1 and (v) 1:0. Fractions containing desired material were combined and concentrated in vacuo to afford Example 9 (0.013g). LCMS showed MH^+ = 357; T_{RET} = 2.89min.

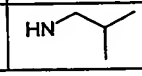
Example 10: N-cyclohexyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



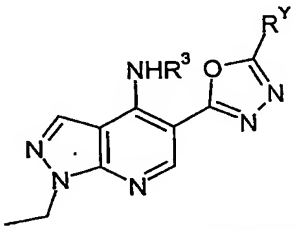
Example 10 NHR^3 = 

Intermediate 13 (0.016g, 0.055 mmol) was dissolved in anhydrous acetonitrile (1ml). Cyclohexyl amine (0.007ml, 0.061 mmol) was then added, followed by diisopropylethyl amine (0.05ml, 0.29 mmol) and the mixture was stirred under nitrogen at 75°C for 16h. The mixture was concentrated in vacuo and partitioned between DCM and water. The organic phase was concentrated in vacuo and applied to an SPE cartridge (silica, 1g), which was eluted sequentially with a gradient of EtOAc: cyclohexane (i) 1:16, (ii) 1:8, (iii) 1:4, (iv) 1:2 and (v) 1:1. Fractions containing desired material were combined and concentrated in vacuo to afford Example 10 (0.015g). LCMS showed MH^+ = 355; T_{RET} = 3.59min.

Similarly prepared using the same or similar number of moles of reagents and volumes of solvents was the following:

	NHR^3	Starting amine	MH^+ ion	T_{RET}(min)
Example 11		Isobutyl amine	329	3.40

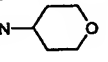
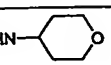
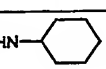
Example 12: 1-Ethyl-N-isobutyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine

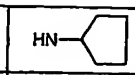
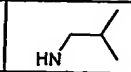
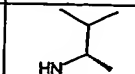
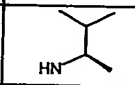
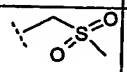
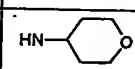
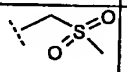
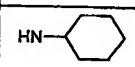
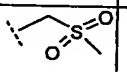
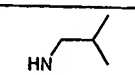
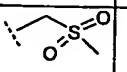
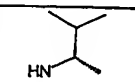
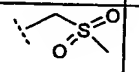
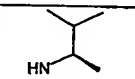


Example 12 R^Y = Me, NHR^3 = 

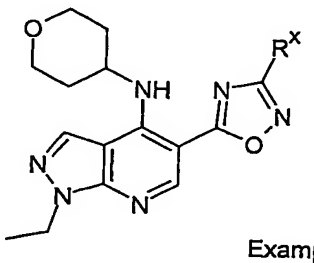
Intermediate 12 (0.026g, 0.1 mmol) was dissolved in ethanol (1.5ml) and treated with a solution of isobutylamine (0.007g, 0.1 mmol), also in ethanol (1ml). The mixture was then treated with diisopropylethyl amine (0.075 ml, 0.4 mmol, 4 mole equivalents) and stirred at 75°C for 16h. The mixture was concentrated in vacuo and applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) chloroform, (ii) Et_2O and (iii) methanol. Fractions containing desired material were combined and concentrated in vacuo to afford Example 12 (0.024g). LCMS showed $MH^+ = 301$; $T_{RET} = 2.90$min

Similarly prepared using the same or similar number of moles of reagents and volumes of solvents were the following:

	R^Y	NHR^3	Starting material	Amine reagent	MH^+ ion	T_{RET} (min)
Example 13	Me		Intermediate 12	Cyclohexylamine	327	3.12
Example 14	Me		Intermediate 12	4-Amino tetrahydropyran	329	2.49
Example 15	Me		Intermediate 12	(R)-(-)-3-methyl-2-butylamine	315	3.00
Example 16	Me		Intermediate 12	(S)-(-)-3-methyl-2-butylamine	315	3.00
Example 17	^{t}Bu		Intermediate 14	4-Amino tetrahydropyran	371	2.99
Example 18	^{t}Bu		Intermediate 14	Cyclohexylamine	369	3.64

Example 19	^{t}Bu		Intermediate 14	Cyclopentylamine	355	3.48
Example 20	^{t}Bu		Intermediate 14	Isobutylamine	343	3.43
Example 21	^{t}Bu		Intermediate 14	(S)-(-)-3-methyl-2-butylamine	357	3.53
Example 22	^{t}Bu		Intermediate 14	(R)-(-)-3-methyl-2-butylamine	357	3.53
Example 23			Intermediate 15	4-Amino tetrahydropyran	407	2.44
Example 24			Intermediate 15	Cyclohexylamine	405	3.00
Example 25			Intermediate 15	Isobutylamine	379	2.81
Example 26			Intermediate 15	(S)-(-)-3-methyl-2-butylamine	393	2.90
Example 27			Intermediate 15	(R)-(-)-3-methyl-2-butylamine	393	2.91

Example 28: 1-Ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



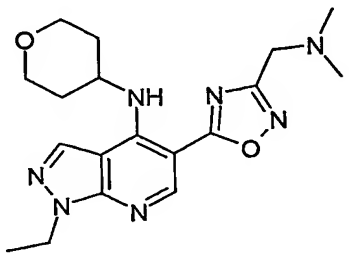
Example 28 R^X = Me

A solution of Intermediate 16 (0.05g, 0.157 mmol) in ethanol (2ml) was stirred over powdered 4Å molecular sieves (0.30g) and treated with a solution of Intermediate 9 (0.059g, 0.8 mmol) and sodium ethoxide (0.027g, 0.4 mmol) in ethanol (1ml). The mixture was heated at reflux for 18h under nitrogen, then cooled and filtered. Following concentration of the filtrate in vacuo, the residue was applied to an SPE cartridge (silica, 5g) which was eluted with cyclohexane : EtOAc (1:1). Fractions containing desired material were combined and concentrated in vacuo to afford Example 28 (0.024g). LCMS showed $MH^+ = 329$; $T_{RET} = 2.86$ min.

Similarly prepared using the same or similar number of moles of reagents and volumes of solvents were the following:

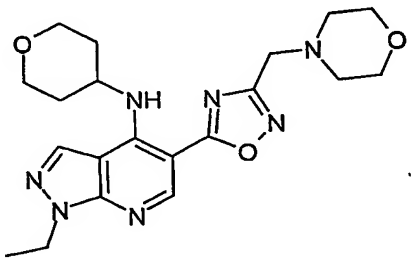
	R^X	Starting Amidoxime	MH^+ ion	T_{RET} (min)
Example 29	CH_2OMe	Intermediate 22	359	2.78

Example 30: 5-{3-[(Dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Intermediate 16 (0.05g) in ethanol (2ml) was stirred over powdered 4Å molecular sieves (0.30g) and treated with a solution of Intermediate 23 (0.094g) and sodium ethoxide (0.027g) in ethanol (1ml). The mixture was heated at reflux for 18h under nitrogen, then cooled and filtered. Following concentration of the filtrate in vacuo, the residue was applied to an SPE cartridge (silica, 5g) which was eluted with 2-5% methanol in DCM. Fractions containing desired material were combined and concentrated in vacuo, then applied to a further SPE cartridge (aminopropyl, 1g) which was eluted with methanol to afford Example 30 (0.02g). LCMS showed $MH^+ = 372$; $T_{RET} = 2.10$ min.

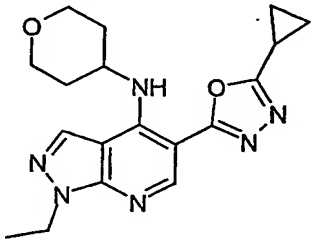
Example 31: 1-Ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Intermediate 16 (0.05g) in ethanol (2ml) was stirred over powdered 4Å molecular sieves (0.30g) and treated with a solution of Intermediate 24 (0.128g) and sodium ethoxide (0.027g) in ethanol (1ml). The mixture was heated at reflux for 18h under nitrogen, then cooled and filtered. Following concentration of the filtrate in vacuo,

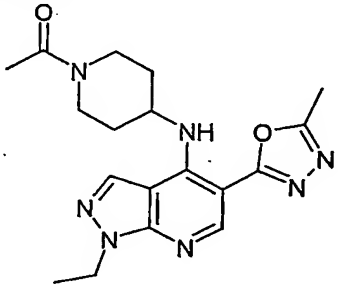
the residue was applied to an SPE cartridge (silica, 5g) which was eluted with 2-5% methanol in DCM. Fractions containing desired material were combined and concentrated in vacuo to afford Example 31 (0.025g). LCMS showed $MH^+ = 415$; $T_{RET} = 2.46$ min.

Example 32: 5-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



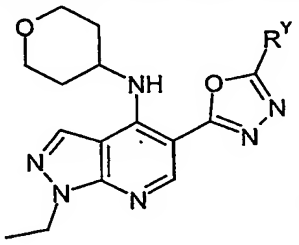
A solution of Intermediate 20 (0.020g) in THF (0.2ml) was treated with Burgess reagent (0.026g) and heated in a microwave at 120°C (100W) for 5min. The mixture was concentrated by evaporation under a stream of nitrogen and the residue applied to an SPE cartridge (silica, 1g) which was eluted with 2% methanol in DCM to afford Example 32 as a white solid (0.014g). LCMS showed $MH^+ = 355$; $T_{RET} = 2.78$ min.

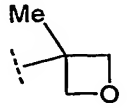
Example 33: N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 12 (0.03g) was dissolved in acetonitrile (2ml) and treated with DIPEA (0.1ml) and Intermediate 25 (0.022g). The mixture was stirred at 85°C for 18h then concentrated in vacuo and partitioned between DCM and water. The layers were separated and the organic layer concentrated in vacuo, then purified by mass directed autoprep HPLC to afford Example 33 (0.01g). LCMS showed $MH^+ = 370$; $T_{RET} = 2.48$min.

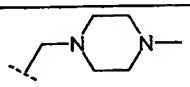
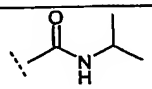
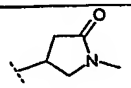
Example 34: 1-Ethyl-5-[5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



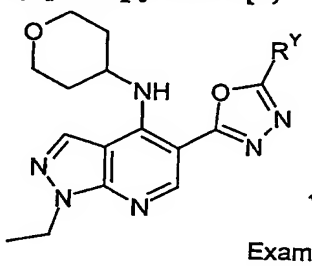
Example 34 R^Y = 

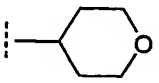
A solution of Intermediate 19 (0.05g, 0.133 mmol), TBTU (0.045g, 0.14 mmol) and DIPEA (0.1ml, ca. 0.5 mmol) in DMF (1ml) was stirred at room temperature under nitrogen for 5 min. A solution of Intermediate 26 (0.024g, 0.21 mmol) in DMF (1ml) was then added and stirring continued for 18h. Reaction was found to be incomplete after this time so a further portion of Intermediate 26 (0.012g, 0.10 mmol) was added and stirring continued under nitrogen for a further 18h. The mixture was concentrated in vacuo then the residue applied to an SPE cartridge (aminopropyl, 2g), which was eluted with methanol (2x3ml). Fractions containing desired material were concentrated in vacuo. The partially purified intermediate was taken forward without further characterisation and was dissolved in THF (0.5ml) then treated with Burgess reagent (0.025g, ca. 0.1 mmol). The mixture was heated under microwave conditions at 120°C (120W) for 5 min. The mixture was then concentrated in vacuo and purified by mass directed autoprep HPLC to afford Example 34 (0.006g). LCMS showed $MH^+ = 385$; $T_{RET} = 2.65$min.

Similarly prepared using the same or similar number of moles of reagents and volumes of solvents were the following:

	R^Y	Starting Acid	MH^+ ion	T_{RET} (min)
Example 35		Intermediate 27	427	2.14
Example 36		Intermediate 28	400	2.87
Example 37		Intermediate 29	412	2.39

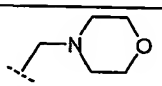
Example 38: 1-Ethyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine



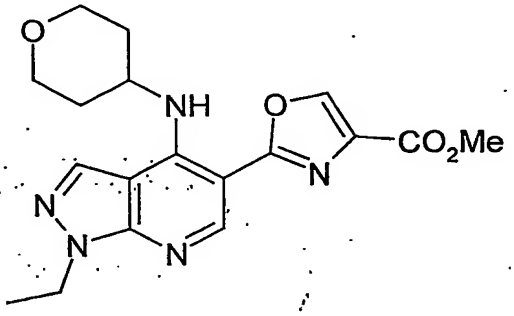
Example 38 R^Y = 

A solution of Intermediate 19 (0.05g, 0.133 mmol), TBTU (0.045g, 0.14 mmol) and DIPEA (0.1ml, ca. 0.5 mmol) in DMF (1ml) was stirred at room temperature under nitrogen for 5 min. A solution of Intermediate 30 (0.018g, 0.14 mmol) in DMF (1ml) was then added and stirring continued for 18h. Reaction was found to be incomplete after this time so a further portion of Intermediate 30 (0.009g, 0.07 mmol) was added and stirring continued under nitrogen for a further 18h. The mixture was concentrated in vacuo then the residue applied to an SPE cartridge (aminopropyl, 2g), which was eluted with methanol (2x3ml). Fractions containing desired material were concentrated in vacuo. The partially purified intermediate was taken forward without further characterisation and was dissolved in THF (0.5ml) then treated with Burgess reagent (0.025g, ca. 0.1 mmol). The mixture was heated under microwave conditions at 120°C (120W) for 5 min. Reaction appeared incomplete so a further portion of Burgess Reagent (0.012g, ca. 0.05 mmol) was added and the mixture heated under microwave conditions at 140°C (120W) for a further 10 min. The mixture was then concentrated in vacuo and purified by mass directed autoprep HPLC to afford Example 38 (0.006g). LCMS showed $MH^+ = 399$; $T_{RET} =$ 2.64min.

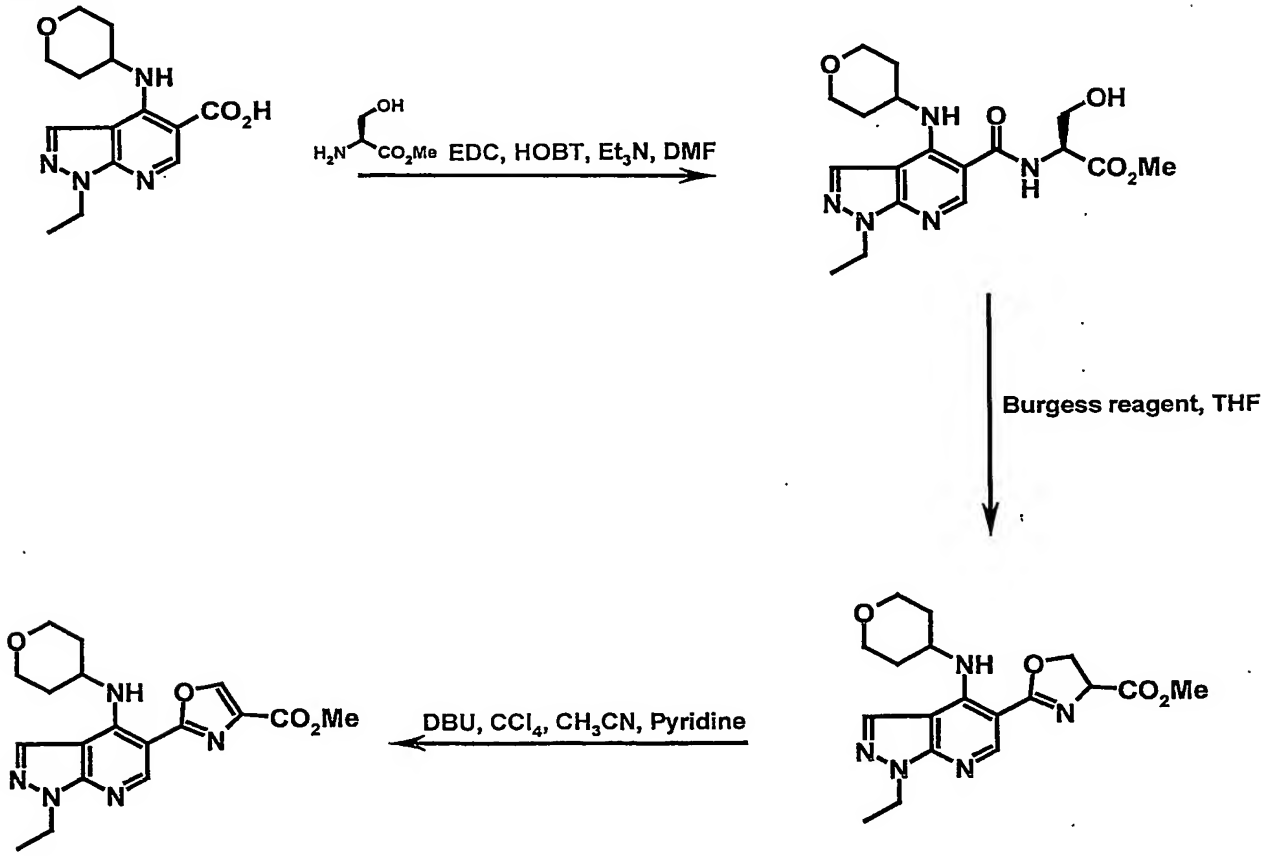
Similarly prepared using the same or similar number of moles of reagents and volumes of solvents were the following:

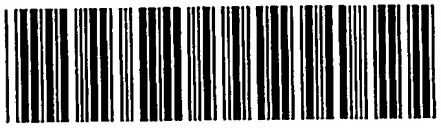
	R^Y	Starting Acid	MH^+ ion	T_{RET} (min)
Example 39		Intermediate 31	414	2.44
Example 40	CH_2O^tBu	Intermediate 32	401	2.98

Example 41: Methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3-oxazole-4-carboxylate



The compound of Example 41 was synthesised using the following route, reagents and solvents:





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